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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/916,140	08/21/1997	MATTHEW P. SCOTT	CIBT-P04-203	2613

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	33

DATE MAILED: 05/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/916,140	SCOTT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 61-77 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 61-77 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/13/02 has been entered.

A preliminary amendment was received and entered as Paper No. 31 on 3/13/02.Claims 61-77 are pending and under consideration in this Office Action.

Priority

This case is a continuation in part of 08/656,065, filed 5/31/96, which is a continuation in part of 08/545,406, filed 10/6/95, which is a continuation in part of 08/319,745, filed 10/7/94. However, the claimed invention finds no support in the disclosures of 08/545,406 or 08/319,745, thus the effective filing date for the instant claims is considered to be 5/31/96.

Compliance With Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Although the Application contains a Sequence Listing, there is no computer-readable form associated with the application. It is noted that this application claims priority from 08/656,065, 08/545,406, and 08/319,745, and that at least one of these cases had a CRF. However, the instant application contains no statement directing the PTO to use the CRF from any of these parent applications. MPEP 2421.02(e) reads:

> (e) A copy of the "Sequence Listing " referred to in paragraph (c) of this section must also be submitted in computer readable form in accordance with the requirements of § 1.824. The computer readable form is a copy of the "Sequence Listing " and will not necessarily be retained as a part of the patent application file. **If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Patent and Trademark Office, reference may be made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application if the computer readable form in the other application was compliant with all of the requirements of these rules. The new application shall be accompanied by a letter making such reference to the other application and computer readable form, both of which shall be completely identified. In the new application, applicant must also request the use of the compliant computer readable "Sequence Listing " that is already on file for the other application and must state that the paper copy of the "Sequence Listing " in the new application is identical to the computer readable copy filed for the other application.**

Emphasis added.

Applicant must provide:

An initial computer readable form (CRF) copy of the "Sequence Listing".

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

OR

A statement directing the PTO to use a CRF from another Application on file at the PTO.

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

PatentIn Software Program Support

Technical Assistance.....703-287-0200

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Specification

The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See page 7, line 20. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Rejections Withdrawn

The rejections of claims 61-77 for lack of enablement is withdrawn in view of Applicant's arguments, particularly the assertion that "whether an agent identified by the methods of this invention is ultimately suitable as a therapeutic *product* is not the standard for enablement of the full scope of the claims." The Office maintains the position that the

specification fails to enable methods of therapy, but concedes that a method of administering an agent to a patient is enabled, for example, as an extension of a screening assay such as in a clinical trial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 61-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed, invention for the reasons of record in Paper Nos. 18 and 25.

Claims 62 and 72-75 are drawn to methods wherein agents are contacted with a cell having a patched loss of function phenotype in order to identify agents which decrease hedgehog signal transduction in the cell.

The specification discloses at page 20, lines 27-29 an assay in which agents are added to a cell which lacks functional patched gene product, and the ability of the cell to reproduce functional patched gene product is determined. There is no other support for the claimed method in the specification. However, the claimed method encompasses a variety of other methods

which do not require the production of a functional patched gene product. Because patched is part of signaling pathway, mutations in other pathway proteins can interfere with the ability of patched to exert its function, and would therefore cause a patched loss-of-function phenotype. The specification fails to contemplate the use of such cells in the claimed method. Further, the claims encompass methods of identifying agents which reverse patched phenotype by duplicating patched function in ways other than the production of functional patched gene product, *i.e.* by stimulating or inhibiting the function of the pathway at a point downstream of patched. However, the specification fails to contemplate any method of restoring patched function to a cell lacking that function other than by reproducing functional patched protein in the cell. For this reason the scope of the claim which extends beyond decreasing hedgehog signal transduction by means of adding an agent which reproduces functional patched protein constitutes new matter.

Claims 61 and 63-77 are methods which require a cell that expresses a wild type patched protein and is recombinantly modified to comprise a reporter construct. The genus of such cells reasonably includes cells which naturally express wild type patched protein from endogenous alleles without the aid of any recombinant patched expression constructs, as well as cells which express functional patched protein only because they carry an expression vector encoding patched. The specification supports an embodiment of the invention in which a patched expression vector is introduced into a cell under conditions which allow expression of patched. The specification provides no support for the use of cells which lack such an expression vector. See page 20, lines 21-24. Thus the claims introduce new matter.

Claims 63-71, 76 and 77 recite a method step in which the amount of reporter gene expression in a first cell is compared to the amount of reporter gene expression in a second cell, wherein the second cell does not express a wild type patched protein. The specification fails to support this embodiment, thus it represents new matter.

Response to Arguments

Applicant's arguments filed 3/13/02 have been fully considered to the extent that they apply to the rejection set forth above, but they are not persuasive. At page 6 of the response Applicant maintains the arguments of record in Paper No. 24. These arguments are unpersuasive for the reasons of record in Paper No. 25.

The claim amendments of Paper No. 31 do not affect the rejection because they do not limit the scope of the claims to the material in the specification as filed. Support for the claimed invention appears to be limited to two sentences in the specification. See page 20, lines 27-29. This passage requires that a candidate agent is "added to a cell that lacks functional *ptc*, and screened for the ability to reproduce *ptc* in a functional assay." At page 1, line 23 "*ptc*" is defined as the *patched* gene product. Hence the specification supports a method in which an agent causes reproduction of the patched gene product. As discussed above, the instant claims are not limited to this scope, but instead encompass embodiments in which hedgehog signal transduction is decreased by any mechanism possible, including inhibition of pathway steps downstream of patched. Thus the claims introduce new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-71, 76 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63-71, 76 and 77 are indefinite because it is unclear how one would identify a test agent that decreases hedgehog signal transduction by comparing the amount of reporter gene expression in the first recited cell to the amount of reporter gene transcription in the second recited cell.

The claims recite two distinct methods for identifying an agent that decreases hedgehog signal transduction. This rejection is directed to the second method. In this method the identification step requires comparison of reporter gene expression in a first cell with reporter gene expression in a second cell. The first and second cells comprise reporter constructs that are driven by hedgehog signal transduction. The first and second cells differ only in that the second cell does not express a functional wild type patched protein. Given that the function of patched is to decrease hedgehog signal transduction, one would expect that, in the absence of any agent, the level of hedgehog signal transduction in the first cell should be less than that in the second cell. It is therefore unclear how the comparison step leads to the identification of agents that decrease hedgehog signal transduction.

Claim 65 is indefinite because it recites "the amount of reporter gene protein" without proper antecedent basis. Claim 63, from which claim 65 depends, does not require that the reporter gene product must be a protein. It is suggested that the word "a" should be inserted between the words "of" and "reporter" in claim 65.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 61-63, 65, 68, 70, 72, and 74-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al (Cell (2/1995) 80: 553-562.

Li teaches a method of inhibiting hedgehog signal transduction by contacting cells with a nucleic acid encoding constitutively active cAMP-dependent protein kinase (PKA). The cells may comprise wild type or patched protein, or may have a patched loss of function phenotype. See entire document, especially paragraph bridging columns 1 and 2 on page 557, and Fig. 7 on page 558, especially panels D and E. The reporter gene can be considered to be ptc or ptc^s, each of which is operatively linked to patched transcription control elements. The amount of reporter

is measured with an anti-ptc antibody. See Fig. 7. The nucleic acid can be considered to be in a pharmaceutically acceptable excipient in that it is dissolved in water. The fly embryos receiving the PKA expression construct can be considered to be patients.

Thus Li anticipates the claims.

Claim 61 is rejected under 35 U.S.C. 102(a) as being anticipated by either one of Noveen et al (Biochem. Biophys. Res. Comm. (2/1996) 219: 180-185) or Hammerschmidt et al (Genes Dev. (3/1996) 10: 647-658).

Noveen teaches a method of inhibiting sonic hedgehog signal transduction in vertebrate skin by treating cultured explants with cAMP. Addition of cAMP results in a decrease in sonic hedgehog expression, which in turn results in a decrease in sonic hedgehog-mediated signal transduction in cells of the tissue explant. See abstract.

Thus Noveen anticipates the claim.

Hammerschmidt teaches a method of inhibiting hedgehog signal transduction in fish embryos by contacting cells with an mRNA encoding a constitutively active form of PKA. Hedgehog signal transduction was inhibited even in the presence of coinjected mRNAs encoding sonic hedgehog or Indian hedgehog. See entire document, especially abstract and page 653, column 2, lines 7-16.

Thus Hammerschmidt anticipates the claim.

Conclusion

No claim is allowed. Claims 64, 66, 67, 69, 71, and 73 are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER